PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference P1217PCT-III	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2004/006471	International filing date *(day/month/year)* 16 June 2004 (16.06.2004)	Priority date *(day/month/year)* 24 June 2003 (24.06.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ACTELION PHARMACEUTICALS LTD.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 03 January 2006 (03.01.2006)
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

PCT

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/006471	16.06.2004	24.06.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/4152, A61K31/4155, C07D231/34, C07D231/36, A61P7/02, C07D401/04, C07C47/575, C07C47/542,

Applicant
ACTELION PHARMACEUTICALS LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Seymour, L Telephone No. +49 89 2399-8694

Form (PCT/ISA/237) (Cover Sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/006471

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. all claims with respect to prodrugs and claims 1-17 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 1-17 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. all claims with respect to prodrugs

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-32

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	32
	No:	Claims	1-31
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-32
Industrial applicability (IA)	Yes:	Claims	18-32
	No:	Claims	

2. Citations and explanations

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/006471

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

The present claims do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The functional term "prodrug" does not enable the skilled person to determine which technical features are necessary to perform the stated function. It is thus unclear which specific compounds fall within the scope of said claim. A lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search did not include prodrugs of the compounds of formula I or III.

Claims 1-17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Claims 25-27 have only been searched in as far as they are dependent on claim 18 (see Item VIII).

Re Item IV

This Authority considers that there are two inventions covered by the claims indicated as follows:

I: Claims 1-32 directed to pyrazolidine-3,5-diones useful in the treatment of vascular diseases, and uses, syntheses and corresponding pyrazolidine-3,5-dione intermediates thereof.

II: Claim 33 directed to the provision of further benzaldehydes.

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

According to the PCT Guidelines, III-10.18(b), unity of invention shall be considered to be present in the context of intermediate and final products where the following two conditions are fulfilled:

- the intermediate and final products have the same essential structural element, in that:
  (1) the basic chemical structures of the intermediate and the final products are the same, or
  (2) the chemical structures of the two products are technically closely interrelated, the intermediate incorporating an essential structural element into the final product,

and

- the intermediate and final products are technically interrelated, this meaning that the final product is manufactured directly from the intermediate or is separated from it by a small number of intermediates all containing the same essential structural element.

The first condition is not considered to be fulfilled by claim 33. In this claim a large number of individual benzaldehydes are listed which cannot be considered to be of the same basic chemical structure as 4-(arylmethyene)-pyrazolidine-3,5-diones of present formula I. The only mandatory feature of the structure of formula I contributed by the present benzaldehydes is the methylene group. The claimed benzaldehydes cannot therefore be viewed as incorporating an essential structural element into the final product. This is emphasised by the fact that the claimed benzaldehydes cannot be straightforwardly summarised in the form of a formula which clearly incorporates a structurally distinctive portion of the product, but rather a heterogeneous list of single compounds is claimed differing in the details of the substitution at the benzene moiety. The requirement of a technical relationship with the remaining claims involving special technical features as defined in Rule 13.2 is therefore not met.

Re Item V

1. Reference is made to the following documents:

   D1: CA-A-2012634 D2: WO-A-02102359
   D3: WO-A-0109121

2. With the exception of claim 32, the subject-matter of the present claims is not new in the sense of Article 33(2) PCT:

2.1 Documents D1 and D2 disclose 4-(arylmethyene)-pyrazolidine-3,5-diones of present formula I (D1, claim 1 and first structure on p. 17; D2, claim 1 and examples) and their use in the treatment of diseases such as cardiovascular diseases (see D1, title and claim 10; D2, p. 17, lines 2-3), which fall within the scope of the diseases defined in present claim 1.

2.2 There are regions of overlap between the general formula of claim 18 of the present application and those of D1-D3 (see D1, claim 1; D2, claims 1 and 13; D3, claims 18-20, whereby the compounds such as those disclosed in claims 19 and 20 may act as prodrugs, cf. Item III). For a region of overlap with a known group to be considered novel, it must provide a technical teaching not contained in the prior art. In the present case, such a technical teaching could lie in the fact that the benzylidine group is substituted at positions 2, 3 and 4. However, this structural feature is already present in D2 and D3 (D2, example 70; D3, p. 142, line 3). It is therefore not apparent what might constitute a novel technical teaching of claim 18 over the disclosures of D2 or D3, and these overlapping regions are considered to be novelty-destroying.

3. Inventive step (Article 33(3) PCT)

Given the disclosure in D1 and D2 of 4-(arylmethyene)-pyrazolidine-3,5-diones and their use in the treatment of diseases such as cardiovascular diseases, thrombosis and ischemia, an inventive step cannot be acknowledge for the present claims.

4. Industrial applicability (Article 33(4) PCT)

For the assessment of the present claims 1-17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

	Publication no.	Priority date	Filing date	Publication date
D4:	WO-A-03074550	01.03.02	03.03.03	12.09.03

Excluding a specific example of D4 from claim 18 by means of a proviso (cf. p. 25, column 3, line 2) cannot reestablish novelty, since the remaining region of overlap between claim 18 and general formula I of D4 does not provide a novel technical teaching over prior art D4.

Re Item VIII

Although claims 25-27 have been drafted as separate independent claims, they appear to comprise all the features of claim 18. The former are therefore not appropriately formulated as claims dependent on the latter (Article 6 and Rule 6.4 PCT).